Refer to: Sack RL, Shore JH: Psychopharmacology in medical practice—The benefits and the risks (Medical Progress). West J Med 134:223-233, Mar 1981

Medical Progress

Psychopharmacology in Medical Practice — The Benefits and the Risks

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Psychopharmacology has become a major approach to treatment in primary medical care. However, combined psychiatric and medical illness can give rise to some challenging diagnostic problems. Furthermore, drug treatment of patients with such illnesses can involve important drug-disease interactions and drug-drug interactions. One should keep in mind the issues that arise when an emotionally troubled patient would benefit from a psychotropic drug but a concurrent medical illness complicates this treatment. An awareness of both the medical and psychiatric issues involved may make successful treatment possible.

PSYCHOPHARMACOLOGY HAS BECOME a major part of medical practice.[1-3] A survey by Parry and associates showed that 22 percent of the population had used a prescription psychotropic drug in the preceding year and that most of these drugs were prescribed by nonpsychiatric physicians.[4] Diazepam is still the most frequently prescribed drug in the world. Tricyclic antidepressants are increasingly prescribed by nonpsychiatric physicians, as well as by psychiatrists.

In recent years concern has been raised about this heavy use of psychopharmacology, some critics alleging that we are becoming an "overmedicated society."[5] Perhaps in response, the use of benzodiazepines appears to be in decline.[6] A number of studies have been conducted to gauge the extent of possible misuse of prescription psychotropic drugs and have concluded that, while individual instances of abuse are certainly a problem, most patients use prescription psychotropic drugs appropriately and are appreciative of the benefits derived.[7-9]

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Why are psychopharmacologic treatments so popular with general physicians? Studies of primary care practices indicate that a sizable number of patients complain to their physicians of mental and emotional difficulties. Indeed, it appears that more people seek help for these problems from their primary physicians than from special mental health clinics.[10] Psychotropic drugs have proved effective for many common emotional illnesses. The use of psychopharmacology fits more naturally into a medical practice than other psychiatric treatments such as formal psychotherapy.

Other reasons for the heavy use of psychopharmacology may not be easily justifiable. Physicians may reach for a prescription pad rather than hear out the concerns of a troubled patient. They may use drugs to modify symptoms when more fundamental changes are needed.

Another criticism of the use of psychopharmacologic drugs is that they are prescribed by many physicians who do not seem to devote the kind of attention to the indications, dosage schedules and side effects as they would with other drugs. For example, one study showed that most patients treated for depression with a tricyclic antidepres-

sant were receiving an inadequate dose for an extended period of time even though their symptoms were not responding.[11] New developments in the standardization of psychiatric diagnosis and in the understanding of pharmacokinetics of psychopharmacologic drugs now make the use of these drugs more rational and less empirical than was once the case.

In this paper we will address the issue of appropriate use of psychopharmacology in the *medical context.* As for any class of drugs, appropriate use depends on a knowledge of *diagnosis, indications* for drug treatment and potential *risks.* For a medically ill patient, each of these facets of psychopharmacology is more complex because the issues of physical symptoms, diseased organs and drug-drug interactions have to be considered alongside the psychiatric problems under treatment.

Diagnosis and Indications

The chances of successful drug treatment are increased and the risks of abuse are diminished when a specific psychiatric diagnosis can be made and the most appropriate drug for that syndrome is selected. When psychotropic drugs are used to counteract *symptoms,* the effects are much more unpredictable. A discussion of the differential diagnosis of psychiatric illness is well beyond the scope of this paper; nevertheless, a few points about psychiatric diagnosis in the context of medical illness are important in this discussion.

The task of making a specific and relevant psychiatric diagnosis has been made easier for psychiatrists and nonpsychiatrists alike with the adoption of the *Diagnostic and Statistical Manual —Third Edition,* the DSM-III.[12] This document, which has been a major preoccupation among psychiatrists for the past six years, has now been officially adopted by the American Psychiatric Association. It contains explicit, operationally defined, diagnostic criteria for all psychiatric diagnoses. For an example, see Table 1 which lists the diagnostic criteria for a major depressive episode.

In some cases—for example, depression—the formal diagnostic criteria correlate highly with the factors found to predict successful drug therapy. In other words, the more closely the patient fits the diagnostic criteria, the more likely he will respond to pharmacological treatment.[13] If he lies in the *gray zone,* the probability of successful treatment diminishes. If drug treatment is contemplated, it can be useful to review the diagnostic criteria for the entity to be treated before embarking on a course of therapy. (The DSM-III can be purchased from the American Psychiatric Association.*)

*American Psychiatric Association, Publication Sales, 1700 18th Street, N.W., Washington, DC 20009. Price: $20.00 paperback; $25.00 casebound.

TABLE 1.—*Diagnostic Criteria for Major Depressive Episode**

A. Dysphoric mood or loss of interest or pleasure in all or almost all usual activities and pastimes. The dysphoric mood is characterized by symptoms such as the following: depressed, sad, blue, hopeless, low, down in the dumps, irritable. The mood disturbance must be prominent and relatively persistent, but not necessarily the most dominant symptom, and does not include momentary shifts from one dysphoric mood to another dysphoric mood, e.g., anxiety to depression to anger, such as are seen in states of acute psychotic turmoil. (For children under six, dysphoric mood may have to be inferred from a persistently sad facial expression.)

B. At least four of the following symptoms have each been present nearly every day for a period of at least two weeks (in children under six, at least three of the first four):
   (1) poor appetite or significant weight loss (when not dieting) or increased appetite or significant weight gain (in children under six, consider failure to make expected weight gains);
   (2) insomnia or hypersomnia;
   (3) psychomotor agitation or retardation (but not merely subjective feelings of restlessness or being slowed down) (in children under six, hypoactivity);
   (4) loss of interest or pleasure in usual activities, or decrease in sexual drive not limited to a period when delusional or hallucinating (in children under six, signs of apathy);
   (5) loss of energy; fatigue;
   (6) feelings of worthlessness, self-reproach, or excessive or inappropriate guilt (either may be delusional);
   (7) complaints or evidence of diminished ability to think or concentrate, such as slowed thinking, or indecisiveness not associated with pronounced loosening of associations or incoherence;
   (8) recurrent thoughts of death, suicidal ideation, wishes to be dead or suicide attempt.

C. Neither of the following dominate the clinical picture when an affective syndrome is absent (i.e., symptoms in critera A and B above):
   (1) preoccupation with a mood-incongruent delusion or hallucination;
   (2) bizarre behavior.

D. Not superimposed on either schizophrenia, schizophreniform disorder or a paranoid disorder.

E. Not due to any organic mental disorder or uncomplicated bereavement.

*Reprinted by permission from Diagnostic and Statistical Manual of Mental Disorders, Third Edition. Washington, DC, The American Psychiatric Association, 1980, pp 213-214.

Patients with significant medical illness who have symptoms that overlap with the symptoms of a psychiatric disorder present a diagnostic challenge. For example, a patient with carcinoma may have anorexia, a sleep disturbance and a sad affect. These symptoms may be explained on the basis of the medical diagnosis or with a diagnosis of depression (Table 1). One helpful strategy in differentiating these possibilities is to look for the remaining elements of a depressive syndrome; for example, difficulty concentrating, guilt, diurnal variation and the like. In some difficult cases there is no choice but to begin a clinical trial of psychotropic medication. It can be a significant error to withhold treatment from a medically ill patient whose psychiatric symptoms may seem "understandable" in the context of his physical illness but who is found to obtain considerable relief with carefully managed drug therapy.

While a good many patients report overt emotional complaints to their primary physicians, a sizable group complain of physical symptoms which, upon investigation, are medically unexplained and are presumed to be psychogenic in origin. These kinds of complaints frequently are reasons for prescribing psychotropic drugs. Anxiety or depression is hypothesized to underlie the complaints. While this rationale may have merit, there is much less evidence to support pharmacological interventions for such indications than for clear-cut psychiatric syndromes.

However, there are a few fairly well-known clinical entities in which a primary psychiatric disorder is masked by somatic complaints. For example, a psychogenic pain syndrome is often associated with depressive features on psychological testing and is frequently responsive to tricyclic antidepressants; thus, a significant number of such cases may be considered "masked depressions."[14] Another example is "depressive pseudodementia," a disorder of older patients in which affective

TABLE 2.—Antianxiety Agents. *Pharmacological Profile of Factors That May Influence Drug Selection in Medically Ill Patients*

Benzodiazepines	*Sedation*	*Elimination Half-Life*[17]	*Intramuscular Absorption*[18]	*Active Number of Metabolites*[17]	*pH Dependent Intragastric Conversion*[19]	*Representative Brands*
Chlordiazepoxide	2	5-30 hrs	Variable	3	0	Librium
Diazepam	3	20-50 hrs	Variable	1	0	Valium
Oxazepam	2	5-20 hrs	Parenteral form not available	0	0	Serax
Clorazepate	3	30-60 hrs	Parenteral form not available	1	+	Tranxene, Azene
Prazepam	2	20-50 hrs	Parenteral form not available	2	+	Verstran
Lorazepam	2	10-15 hrs	Parenteral form not available	0	0	Ativan
Flurazepam	3	47-100 hrs	Parenteral form not available	1	0	Dalmane

When compared to other drugs of the same class:
1—"least" 2—"intermediate or average" 3—"most"

TABLE 3.—Antidepressant Drugs. *Pharmacological Profile of Factors That May Influence Drug Selection in Medically Ill Patients*

	Sedation[20]	*Anticholinergic Activity*[21]	*Slowed Cardiac Conduction*[22-25]	*Postural Hypotension*[26]	*Elimination Half-Life*[27]	*Type of Amine*	*Metabolism*	*Representative Brands*
Tricyclic Antidepressants								
Imipramine	2	2	3	2	8 hrs	3°	↓	Tofranil
Desipramine	1	1	3	1	17 hrs	2°	↓	Norpramin, Pertofrane
Amitriptyline	3	3	2	3	15 hrs	3°	↓	Elavil, Endep
Nortriptyline	1	1	2	2	27 hrs	2°	↓	Aventyl, Pamelor
Protriptyline	0	2	2	1	78 hrs	2°		Vivactil
Doxepin	3	3	1	3	17 hrs	3°	↓	Sinequan, Adapin
Desmethyldoxepin	..	..	..	..	51 hrs	2°	↓	(Not marketed)
Monoamine Oxidase Inhibitors								
Tranylcypromine	0	1	0	1	1-2 wks*	..		Parnate
Phenelzine	0	1	0	1	1-2 wks*	..		Nardil

When compared to other drugs of the same class:
1—"least" 2—"intermediate or average" 3—"most"

*Time needed for monoamine oxidase activity to be restored.

complaints are masked behind major concerns with the loss of cognitive functions.[15]

Because of these and other less easily classified examples of drug-sensitive disorders hiding behind somatic symptomatology, a trial of psychotropic agents is sometimes warranted even when a specific diagnosis cannot be made. However, in such instances, the attitude of the physician should be that of conducting a clinical trial. The goals of treatment should be stated as clearly as possible in the record and to the patient. The dose of the selected drug should be increased to the therapeutic range and sustained for a planned period of time. If no response is observed, the drug should be tapered and discontinued.

The theme of the foregoing discussion has been the importance of basing intervention on the diagnosis of a specific psychiatric entity. This is true especially for the affective disorders. There is little hope of lifting the pain of a realistic tragedy with an antidepressant. Likewise, lithium will not dampen the euphoria that comes with genuine good fortune.

Notwithstanding, some psychopharmacologic drugs *do* counter symptoms as well as syndromes. For example, the antipsychotic drugs are not only useful in schizophrenia (the most frequent indication), but are useful in the acute manic episode and in psychotic depression. In low doses they can be dramatically effective in the agitated, delirious patient. Antianxiety drugs seem to modify "realistic" anxiety as well as neurotic anxiety; for example, they are quite effective in calming patients before operations.

Some psychopharmacologic drugs have a spectrum of action beyond psychiatric symptoms. For example, the phenothiazine drugs are useful antiemetics; benzodiazepines are useful in the treatment of status epilepticus. Occasionally novel effects for psychotropic drugs are reported which may be an extension of their psychotropic properties or may be quite independent. The prophylactic effect of tricyclic antidepressants in migraine syndrome[16] may be by modification of psychological functioning or may be due to some other property of drugs.

Although treating a psychiatric disorder in the context of a physical illness may sometimes be difficult and, on occasion, risky, the benefits can be important not only for the emotional well-being of the patient, but for the recovery from physical illness as well. Untreated psychiatric problems may place added strain on already diseased organs. Furthermore, a patient who is severely anxious, depressed or psychotic will have great difficulty complying with medical treatment. In assessing the ratio of benefit to risk, one has to include the risk to the physical health of the patient by *not* treating a psychiatric illness, as well as the risk to physical health presented by the side effects of psychotropic drugs.

TABLE 4.—Antipsychotic Drugs. *Pharmacological Profile of Factors That May Influence Drug Selection in Medically Ill Patients*

	Sedation[28]	*Extrapyramidal Side Effects*[28]	*Anticholinergic Activity*[29]	*Postural Hypotension*[28]	*Slowed Cardiac Conduction*	*Representative Brands*
Phenothiazines						
Chlorpromazine	3	2	2	3	..	Thorazine
Thioridazine	3	1	3	3	3	Mellaril
Mesoridazine	3	1	3	3	3	Serentil
Prochlorperazine	2	2	2	2	..	Compazine
Perphenazine	2	2	2	2	..	Trilafon
Trifluoperazine	2	2	2	2	..	Stelazine
Fluphenazine	1	3	2	2	..	Prolixin
Thioxanthene						
Thiothixene	2	2	2	2	..	Navane
Butyrophenones						
Haloperidol	1	3	1	1	..	Haldol
Droperidol	1	3	1	1	..	Inapsine
Dibenzoxazepines						
Loxapine	2	2	2	2	..	Loxitane
Indolics						
Molindone	2	2	2	2	..	Moban

When compared to other drugs of the same class:
1—"least" 2—"intermediate or average" 3—"most"

Risks

Because there is a large amount of information to be included under the potential risks of psychopharmacologic drugs from side effects, drug-disease interactions and drug-drug interactions, this material has been summarized in a number of tables. In Tables 2 through 4 the pharmacological characteristics that might affect the choice of drug from within each class are presented. In Table 5 potential drug-disease interactions are listed (excluding the drug-drug interactions that might result from the drugs typically employed for those diseases). In Table 6 significant drug-drug interactions are listed.

Some general categories of medical patients carry common risk factors. For example, as a general rule pregnant women should not receive medications of any kind unless it is considered essential. Studies have suggested that exposure during pregnancy to lithium leads to an increase in the incidence of the Ebstein malformation of the heart in the newborn,[59] and of cleft palate with benzodiazepine use.[60] Guidelines for minimizing risks of psychopharmacologic treatment during pregnancy can be found in the review by Goldberg and DiMascio.[61] Another category, the elderly, metabolize many drugs more slowly and are more sensitive to side effects.[62] It is wise, as a general rule, to reduce the usual dose to half in patients older than 65 years, at least at the initiation of drug treatment.

Antianxiety Agents

Benzodiazepines are the most prescribed psychotropic drugs in medicine today.[2] They are mainly indicated as antianxiety agents, but they are used as muscle relaxants and anticonvulsants as well. Benzodiazepines are typically somewhat sedative, but the reduction in anxiety is independent of their sedative effects. The mechanism of action of the benzodiazepines is unknown, although current evidence suggests that their effects may be mediated through the GABA (gamma aminobutyric acid) system.[63] Recently, a specific "Valium receptor" has been discovered in the brain, suggesting that these drugs may be interacting with an endogenous neuromodulator that has yet to be defined.[64]

Undoubtedly the tremendous popularity of the benzodiazepines as antianxiety agents derives from their remarkable safety, especially when compared with their predecessors, the barbiturates. The main risk for the benzodiazepines is psychological dependence, and to a much lesser degree, physiological dependence. Again, contrasting them with barbiturates, these risks are significantly less.

The benzodiazepines may disinhibit ordinarily suppressed behavior. For example, patients may be more likely to express hostile feelings and may be more apt to lose emotional control.[65] Some patients find benzodiazepines depressogenic.

It appears to be nearly impossible to commit suicide with benzodiazepines alone, although they potentiate the respiratory depression and other toxic effects of sedative agents such as alcohol and barbiturates.

There are some significant differences in the properties of the available benzodiazepines, although the basic efficacy in the treatment of anxiety is similar. For example, chlordiazepoxide has three active metabolites which are formed in the liver. Therefore, the duration of pharmacological activity can be affected by the rate of hepatic metabolism which can be reduced in liver disease. Flurazepam has a very long duration of action which may account for the lack of rebound insomnia when this drug is used as a nighttime sedative.[66] On the other hand, this long half-life may contribute to significant daytime drowsiness. To help a patient get to sleep during an occasional episode of insomnia, one might chose oxazepam which has a short half-life and no active metabolites. Two of the benzodiazepines, clorazepate and prazepam, are transformed in the stomach to active drugs. This process is dependent on the pH of the stomach and can be inhibited by antacid therapy.[19]

Chlordiazepoxide and diazepam are the only benzodiazepines available for parenteral use; however, intramuscular absorption is variable and thus the oral or intravenous route is preferable. Lorazepam seems to be evenly absorbed intramuscularly, but a parenteral form is not yet available in the United States.[67]

Although the propanediols, such as meprobamate, are also very safe in medically ill patients, they are much more likely to cause withdrawal effects and to be lethal if taken in overdose. For these reasons, they are second-order drugs in the treatment of anxiety.

Tricyclic Antidepressants

Tricyclic antidepressants have potent effects on a number of neurotransmitter systems. They block the synaptic reuptake mechanisms for norepi-

TABLE 5.—*Common Drug-Drug Interactions*

	Benzo-diazepines	*Tricyclic Antide-pressants*	*Pheno-thiazine Anti-psychotics*	*Butyro-phenones*	*Lithium*	*MAO Inhibitors*	*Clinical Implications*
Anticholinergics	0	2	2	1	0	1	*Additive Anticholinergic Effects* Additive anticholinergic effects can cause constipation, paralytic ileus, urinary retention, fever, tachycardia and delirium.[30] Dental caries are a secondary effect of dry mouth.[31] Acute anticholinergic toxicity may be reversed with physostigmine.[32,33]
Antacids	1	1	1	1	0	..	*Diminished Absorption* Antacids may diminish the absorption of phenothiazines[34] and benzodiazepines[35]; also, antacids may inhibit the intragastric conversion of some benzodiazepines.[19]
Sedative hypnotics	2	0	0	0	0	0	*Cross-tolerance* All sedative hypnotic drugs, including barbiturates and alcohol, manifest cross-tolerance with benzodiazepines.
	2	2	2	1	1	0	*Additive Sedative Effects* Most psychotropic drugs produce some degree of sedation which will add to the effects of alcohol or other sedatives.[36]
Opiate analgesics	1	1	1	1	0	3	*Potentiation of Analgesic Activity* Psychotropic drugs can potentiate the analgesic action of opiates.[14,37-39] However, the combination of meperidine (Demerol) and MAO inhibitors can be hazardous.[40]
Antihypertensive drugs							*Inhibition*
Guanethidine	0	2	2	0	0	..	Antihypertensive drugs which depend on "amine pump" uptake into the cell are blocked by
Clonidine	0	2	2	0	0	..	2° amine tricyclics and by chlorpromazine.[41]
Sodium-depleting diuretics	0	0	0	0	3	0	*Lithium Toxicity* Sodium-depleting diuretics stimulate the kidney to retain lithium.[42,43]
Beta-blockers	0	1	1	0	0	..	*Inhibition* Tricyclics and phenothiazines can diminish the effectiveness of beta-blockers.[26]
Pressor amines	0	0	0	0	0	3	*Acute Hypertensive Crisis* Pressor amines, as well as foods containing tyramine, can precipitate an acute hypertensive crisis in patients taking an MAO inhibitor.[44]
Antihistamines							
H_1-blockers	1	1	1	1	1	..	*Additive Sedative Effects* Most psychotropic drugs have some sedative effects.[45]
H_2-blockers	1	1	1	..	..	..	*Mixed* Cimetidine can impair the elimination of benzodiazepines.[46] Tricyclics and phenothiazines have H_2 receptor blocking effects[45] which are probably additive with cimetidine.
Quinidine	0	2	2	..	..	..	*Cardiac Arrhythmias* Additive slowing of cardiac conduction may lead to arrhythmias.[42]

0—No interaction 1—Known interaction but clinical importance variable 2—Interaction usually significant 3—Hazardous interaction
MAO = monoamine oxidase

TABLE 6.—*Drug-Disease Interactions**

	Benzo-diazepines	*Tricyclic Antide-pressants*	*Pheno-thiazine Anti-psychotics*	*Butyro-phenones*	*Lithium*	*MAO Inhibitors*	*Clinical Implications*
Hypertension	T	..	..	..	..	T	Benzodiazepines are reported to be beneficial in mild hypertension.[47] Pargyline (Eutonyl), a MAO inhibitor, is marketed as an antihypertensive.[48]
Cardiac disease							
Arrhythmias	S	T,H	T,H	S	..	..	The quinidine-like effects of tricyclic antidepressants and some phenothiazines (especially thioridazine) may be hazardous in the patient with conduction defects,[22] but beneficial for myocardial irritability.[23,24]
Congestive failure	S	H	H	..	..	..	Tricyclic antidepressants and phenothiazines have been reported to worsen congestive failure.[25]
Coronary vascular	T?,S	H	H	S	..	..	Postural hypotension may reduce coronary perfusion. Benzodiazepines are useful in acute postmyocardial infarction treatment.[49]
Liver disease	H	H	H	H	S	H	Since all psychotropic drugs (except lithium) are partially metabolized in the liver, toxic levels can accumulate in severe liver disease.[50,51]
Kidney disease	H	H	H	H	C	H	Since lithium is excreted entirely by the kidney, it should not be given in renal failure. Other drugs can be given if monitored closely.[52]
Gastrointestinal							
Irritable bowel and "functional" complaints	T	S	S	S	S	S	Tricyclic antidepressants have recently been shown to have strong H_2 receptor blocking activity[44] which may explain the therapeutic effect in peptic ulcer disease.[53]
Peptic ulcer	T	T	S	S	S	S	Antianxiety agents are popular treatments for a variety of gastrointestinal conditions.[54]
Dermatological disease	T	T	T	T	..	..	Psychotherapeutic drugs may help in stress-related eruptions.[55]
Respiratory disease							
Respiratory insufficiency	H	H	H	H	H	..	Most psychotherapeutic drugs have at least some respiratory depressant effects.
Asthma	T	T	T	..	..	..	Psychotropic drugs have been reported to be useful adjuncts.[56]
Neurological							
Cerebral vascular disease	S	H	H	S	..	H	The main risk is postural hypotension leading to inadequate perfusion and stroke.
Migraine	..	T	..	..	..	..	Amitriptyline recently reported as effective prophylaxis in migraine.[16]
Delirium and dementia	H	T,H	T,H	T,H	..	..	Phenothiazines and butryophenones can be quite helpful in organic brain syndromes if used in small doses. If overused, they can intensify confusion.
Chronic pain syndromes	S	T	T	T	..	..	For reviews, see Table 3, references 24-27.
Hematologic							
Leukopenia	..	..	..	..	T?	..	Lithium stimulates leukocyte production.[57]
Pregnancy	H	H	H	H	H	H	All drugs should be considered hazardous.

T—Potentially therapeutic S—Reported as safe H—Potentially hazardous C—Contraindicated

*Excluding potential drug-drug interactions for drugs typically used in these conditions.

nephrine and serotonin. They are strongly anticholinergic (antimuscarinic) and antihistaminic. The reuptake blockade has been invoked to explain their therapeutic effects since it fits the catecholamine theory of depression;[68] however, there are many reasons to doubt that this action is a sufficient explanation for their antidepressant effects.[69]

The tricyclics can be subdivided chemically into the tertiary and secondary amine categories (See Table 3). The tertiary amines are more active with the serotonin reuptake system while the secondary amines differentially affect the noradrenergic system. It has been suggested that this difference may be important in subcategorizing depressions as *serotonergic* and *noradrenergic* depending on which class of tricyclics is effective.[70] Failure to respond to a secondary amine tricyclic might, at least, prompt a trial with a tertiary, and vice versa. However, since the tertiary drugs are metabolized to secondary tricyclics, this differential neurotransmitter effect is not completely specific.

The risks for a medical patient taking tricyclic antidepressants begin with their autonomic side effects. Anticholinergic manifestations include dry mouth, blurred vision and urinary retention. The postural hypotension typical of these drugs is most likely secondary to alpha-adrenergic blockade. These side effects are mainly a nuisance for healthy patients, but can be very serious for those who are medically ill. For example, postural hypotension may precipitate a vascular accident in a patient with transient ischemic episodes. A syncopal fall in an elderly patient may result in a broken hip with complications. Since there is considerable variation in autonomic side effects among the various available compounds, it is wise to consider the autonomic profile when choosing a drug. Table 3 lists some of the characteristics of tricyclic antidepressants that might influence the choice of a drug, especially in medically ill patients.

Perhaps the most worrisome side effect from the tricyclics is their alleged cardiotoxicity. Considerable controversy has developed in this matter. There is no question that an overdose of tricyclics can lead to arrhythmias, but the danger of these drugs in the usual doses is still debated. One source of risk derives from the effects of these drugs on electrical conduction of the heart. By and large, tricyclics act like quinidine, slowing the conduction time. Such an effect might be safe, indeed therapeutic, in a patient with increased myocardial irritability. On the other hand, for a patient with conduction defects this could lead to complications. Doxepin appears to have the least effect on cardiac conduction and is the drug of choice when this factor is a major consideration.

The monoamine oxidase inhibitors are rarely used in this country. Most physicians in the United States abandoned them after reports of hepatic toxicity (now known to be rare), and the famous "cheese reaction." However, their use was sustained in Great Britain, and problems have been rare. The monoamine oxidase inhibitors may be undergoing a comeback in this country.

Several new classes of antidepressants are under development.[71-76] Clinical trials have shown efficacy which compares favorably with the tricyclics; furthermore, they appear to be safer in many respects. Some of these newer antidepressants may be especially useful for medically ill depressed patients when (and if) the drugs become available in the United States.

Antipsychotics

Antipsychotic activity is closely related to dopaminergic receptor blockade. However, antipsychotic drugs may have anticholinergic (antimuscarinic), antihistaminic and adrenergic blocking effects as well.

The phenothiazine derivatives (chlorpromazine, thioridazine and the like) all produce postural hypotension to some degree. Therefore, when an antipsychotic drug is required in a medically ill patient, haloperidol is frequently preferred. Some antipsychotic drugs, such as thioridazine, have quinidine-like effects similar to the tricyclics and thus must be used with caution in patients with a preexisting conduction defect.

A long-term risk in using the antipsychotic compounds is the occurrence of tardive dyskinesia. For this reason, these compounds should not be employed when other approaches are available; for example, they should not be employed as antianxiety agents as has been sometimes advocated in the past.

Clinical Examples

In the last section of this paper, some examples will be provided of the ways in which thoughtful consideration of the various aspects of psychopharmacological treatment advanced the care of some difficult clinical problems in a general hospital.

CASE 1. A 45-year-old man who had never been in the hospital in his life was admitted with a large myocardial infarction. On the third hospital day he became acutely paranoid, believing that his wife had been unfaithful while he was confined to the hospital. He demanded discharge against advice and was poised to do combat with anyone who challenged him. His cardiac status was quite marginal and there was serious concern that he would not survive if he left the coronary care unit. After a court hold was signed, a dose of droperidol, 5 mg, was administered intravenously. Within a few minutes he was calm and manageable. This was followed by the use of small doses of haloperidol over the next few days. The day after this incident, he apologized to the staff and said he "didn't know what came over him."

Comment. This patient was probably suffering from a mild delirium from the use of sedative agents given routinely to myocardial infarction patients. In addition, the sleep deprivation and unfamiliarity of the coronary care unit environment contributed to his loss of control. By the time he exploded, verbal reassurance was ineffectual and pharmacological intervention was required. Further sedation would have most likely intensified his delirium; therefore, a relatively nonsedating antipsychotic drug was used. Because of his recent myocardial infarction and the need to avoid any hypotensive side effects, a drug from the butyrophenone group was selected. Finally, because of the need for fast intervention, droperidol was selected because of the advantage of intravenous administration.

CASE 2. A 51-year-old police investigator presented with depression and suicidal ideation made more compelling because of his easy access to firearms. Five years before, an operation had been done for extensive coronary vascular disease in which three vessels were bypassed. He had done quite well since the operation except for chronic painful dysesthesias around the site of his sternotomy scar. In collaboration with his cardiologist who obtained serial electrocardiograms, he was treated with doxepin with good results. He noticed that the dysesthesias were greatly diminished with tricyclic therapy.

Comment. Doxepin seemed to be a rational choice in this patient because of its minimal effects on cardiac conduction, although postural hypotension could have been a problem. A bonus from this treatment was the relief from the chronic pain syndrome; this is an effect of tricyclics that may be independent of the antidepressant effect.

CASE 3. A 65-year-old man was moderately demented from a slow-growing astrocytoma which was inoperable. He was irritable, distractable and emotionally labile. Haloperidol, 1 mg twice a day, helped him to focus his thoughts more clearly and to be more sociable with the other patients and with the staff.

Comment. Low doses of antipsychotic drugs can be remarkably effective in helping a mildly demented patient order his or her thoughts more effectively. A common error is to sedate such patients heavily, adding to their confusion.

CASE 4. A 26-year-old woman, a graduate student, had been seen by many doctors for somatic complaints. She suffered periods of shortness of breath, an impending sense of doom, and cardiac palpitations which were both incapacitating and mysterious. After some extensive interviewing, she defined her problem more explicitly as anticipatory anxiety about going to a classroom. She suffered very unrealistic fears that she would lose control in such a setting and humiliate herself. She was prescribed diazepam to take before she went to class. It was highly successful in limiting her symptoms and her somatic complaining ceased.

Comment. Benzodiazepines can be very helpful in cases of panic disorder. This case illustrates how judicious use of the drug minimizes dependence and unwanted side effects. Somatic preoccupation appeared to be secondary to her need to find an explanation for her panic attacks.

CASE 5. A 32-year-old man with a history of Crohn disease was under treatment for a recurrent psychosis. Because of symptoms of depression, a tricyclic antidepressant was added. Over the next week nausea and vomiting developed which he attributed to the "flu." However, when he was examined several days later, he was found to be grossly distended and without bowel sounds. He was admitted to hospital where administration of medications was stopped and he was treated with decompression and intravenously given fluids. He recovered without any need for surgical therapy. He was subsequently treated successfully with an antipsychotic drug with low anticholinergic activity.

Comment. This man probably had a paralytic ileus from the combined anticholinergic side effects of a tricyclic antidepressant and a phenothiazine antipsychotic. Previous surgical procedures

for Crohn disease may have left him with adhesions that contributed to the problem.

Conclusions

Psychopharmacology has become an important part of overall medical care. Given the important role psychotropic drugs play in medical practice, knowledge of their indications, actions and hazards should rank alongside that required for the skillful use of other potent drugs.

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Brand Name Versus Generic

A WOMAN CAME TO ME and said, "I've gone to a generic from a brand-name antidepressant, and I get far fewer side effects." She came in the next week, and was depressed again. Why? The answer is obvious. The Food and Drug Administration has informed us that between brand-named antidepressants, and certainly between generic and brand-named antidepressants, there is not bioequivalence. It certainly is true that each might have exactly the same number of milligrams of amitriptyline, but it is not true that the filler is the same or the amount of compression is the same. In other words, the bioavailability is not the same. This woman had managed to get a generic product that was not bioequivalent to what she had been taking. She first had a reduction of side effects, which she liked; but then there was a recrudescence of depression, which she did not like. So it is important that you stay with the same brand you start with. I am not making a big pitch here for brand name over generic, but . . . if you are going to use a generic product, sometimes it is very difficult to know which manufacturer of the generic product is being used.

—ALAN BROVAR, MD, *Los Angeles*

Extracted from *Audio-Digest Internal Medicine*, Vol. 27, No. 2, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 E. Chevy Chase Drive, Glendale, CA 91206.